台灣癌症醫誌 (J. Cancer Res. Pract.) 1(3), 208-219, 2014 DOI: 10.6323/JCRP.2014.1.3.04

journal homepage:www.cos.org.tw/web/index.asp

Original Article

Preoperative Chemoradiotherapy followed by Surgery in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma: a Single Center Experience in Southern Taiwan

Chien-Ming Lo[1], Yen-Yu Chen[1], Yen-Hao Chen[2], Tai-Jan Chiu[2], Shun-Chen Huang[3], You-Ming Wang[4], Fu-Min Fang[4], Yi-Chun Chiu[5], Ming-Jeng Hsieh[1], Shau-Hsuan Li[2]*, Hung-I Lu[1]*

[1]*Department of Thoracic & Cardiovascular Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[2]*Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[3]*Department of Pathology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[4]*Deaprtment of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[5]*Department of Hepato-Gastroenterlogy, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

Abstract.

Objective: In general, the typical outcome of patients with locally advanced esophageal squamous cell carcinoma is poor. Recently, attempts have been made to improve survival of patients with esophageal cancer using preoperative chemoradiotherapy followed by surgery. The experience of a single center in Southern Taiwan with esophageal squamous cell carcinoma was reviewed to determine which clinicopathologic variables could predict survival.

Methods: One hundred and one patients with diagnosed esophageal squamous cell carcinoma who were treated with preoperative chemoradiotherapy followed by surgery at Kaohsiung Chang Gung Memorial Hospital were retrospectively reviewed. Univariate and multivariate survival analyses were performed using log-rank and Cox proportional hazards models.

Results: Of these 101 patients, 26% (26 of 101) achieved a pathologic complete response to treatment. Univariate analysis revealed that clinical T4 disease and absence of pathologic complete response were significantly associated with worse overall survival and disease-free survival. The 3-year overall survival rates were 50% and 24% in patients with clinical T1~3 and T4 disease, respectively (P = 0.01).The 3-year overall survival rates were 68% and 28% in patients with and without pathologic complete response, respectively (P = 0.001). Multivariate analysis also showed that clinical T4 disease and absence of pathologic complete response were independently associated with inferior overall and disease-free survival.

Conclusions: Clinical T4 disease and absence of pathologic complete response were associated with significantly worse survival in patients with esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy followed by surgery.

Keywords **:** esophageal cancer, squamous cell carcinoma, preoperative chemoradiotherapy, esophagectomy, pathologic complete response

原著論文

局部晚期食道鱗狀上皮細胞癌病患接受術前化學放射治療合併手術：南台灣單一醫學中心的經驗

羅乾鳴[1] 陳彥佑[1] 陳彥豪[2] 邱泰然[2] 黃純真[3] 王友明[4] 方富民[4] 邱逸群[5] 謝敏暐[1] 李劭軒[2]* 呂宏益[1]*

[1] 高雄長庚紀念醫院及長庚醫學大學 胸腔及心臟血管外科
[2] 高雄長庚紀念醫院及長庚醫學大學 血液腫瘤科
[3] 高雄長庚紀念醫院及長庚醫學大學 病理科
[4] 高雄長庚紀念醫院及長庚醫學大學 放射腫瘤科
[5] 高雄長庚紀念醫院及長庚醫學大學 胃腸肝膽科

中文摘要

目的：局部晚期食道鱗狀上皮細胞癌病患的治療結果極差。近年來，術前化學放射治療合併手術常被用來試著改善此類病人預後,，我們回溯高雄長庚醫院使用術前化學放射治療合併手術治療局部晚期食道鱗狀上皮細胞癌病患的臨床經驗並試圖找出可預測病人存活的臨床病理因子。

方法：我們總共回溯了 101 位在高雄長庚診斷食道鱗狀上皮細胞癌病患並接受術前化學放射治療合併手術。單變量存活分析及多變量存活分析分別是使用對數等級檢定(log-rank test)及 Cox 比例風險模型。

結果：在 101 位病人中，有 26 位（26%）達到病理完全反應，單變量存活分析顯示臨床 T4 分期及無法達到病理完全反應的病人有較差的整體存活率及無病存活率。三年整體存活率在臨床 T1~3 分期及臨床 T4 分期的病人分別是 50%及 24% (P= 0.01)。三年整體存活率在有達到病理完全反應的病人及無法達到病理完全反應的病人分別是 68%及 28% (P= 0.001)。多變量存活分析也發現臨床 T4 分期以及無法達到病理完全反應為較差的整體存活率及無病存活率的獨立預後因子。

結論：臨床 T4 分期及無法達到病理完全反應明顯地與局部晚期食道鱗狀上皮細胞癌病患接受術前化學放射治療合併手術後較差的預後相關。

關鍵字: 食道癌、鱗狀上皮細胞癌、術前化學放射治療合併手術、食道切除手術、病理完全反應

INTRODUCTION

Esophageal cancer is the sixth-most common cause of cancer death among men in Asian countries. The major histological types of esophageal cancer are adenocarcinoma and squamous cell carcinoma. Although adenocarcinomas are more prevalent in the United states [1], ninety percent of all esophageal cancer in Asian men is esophageal squamous cell carcinoma, which contrasts with those percentages found in men from western countries [2]. Previous studies [3,4] reported that these two histological tumor types of esophageal cancer exhibit different behavior, and should be analyzed separately.

The majority of patients with esophageal squamous cell carcinoma have locally advanced disease when diagnosed. Esophagectomy combined with lymph node dissection is the main treatment for esophageal squamous cell carcinoma. However, the outcome of patients with locally advanced esophageal squamous cell carcinoma treated with surgery alone is

unsatisfactory, with 5-year survival rate of less than 30% [5-8]. In an attempt to improve these survival rates, a multimodality approach, preoperative chemoradiotherapy followed by surgery, has been advocated to downstage the primary tumor, thus increasing resectability rates and eliminating micrometastases [9,10]. The first randomized controlled trial of patients with esophageal cancer treated with preoperative chemoradiotherapy was reported in 1992 by Nygaard et al. [11], and revealed that preoperative chemotherapy and radiotherapy prolonged patient survival. Since then, several studies [6,7,12] comparing preoperative chemoradiotherapy followed by surgery with surgery alone have showed a survival benefit for preoperative chemoradiotherapy, whereas others have not found any survival benefit by preoperative chemoradiotherapy versus surgery alone [8,13-16]. Most randomized controlled studies of preoperative chemoradiotherapy versus surgery alone do not have enough power to show smaller yet worthwhile survival improvements, particularly if tumors are divided into histological subtypes of squamous cell carcinoma and adenocarcinoma. Therefore, Gebski et al. conducted a meta-analysis and reported that a significant survival benefit was evident for preoperative chemoradiotherapy in patients with esophageal squamous cell carcinoma [17]. Thus, preoperative chemoradiotherapy followed by surgery was gradually applied to clinical practice in our hospital for patients with locally advanced esophageal squamous cell carcinoma. Many of the above-mentioned trials have identified several factors that may contribute to improved survival in patients undergoing preoperative chemoradiotherapy followed by surgery, but little is known as to their application for patients in Southern Taiwan. The aim of the present study was to retrospectively review our experience with 101 esophageal squamous cell carcinoma patients undergoing preoperative chemoradiotherapy followed by surgery and attempt to determine which factors may contribute to improvements in overall survival and disease-free survival.

***Corresponding author:** Hung-I Lu M.D.

*通訊作者：呂宏益醫師

Tel: +886-7-7317123 ext.8008

Fax: +886-7-7354309

E-mail: luhungi@yahoo.com.tw

***Corresponding author:** Shau-Hsuan Li M.D.

*通訊作者：李劭軒醫師

Tel: +886-7-7317123 ext.8008

Fax: +886-7-7354309

E-mail: lee0624@cgmh.org.tw

C-M Lo and Y-Y Chen equally contributed to this article

MATERIALS AND METHODS

Patient Population

Patients with esophageal squamous cell carcinoma who were treated with preoperative chemoradiotherapy followed by surgery from 2000 to 2012 at Kaohsiung Chang Gung Memorial Hospital were retrospectively reviewed. Patients with synchronous cancers were excluded. This study was approved by the institutional review board of Chang Gung Memorial Hospital.

In the present study, 101 patients with esophageal squamous cell carcinoma who were treated with preoperative chemoradiotherapy followed by surgery were identified. Among these 101 patients, 26 (26%) achieved pathologic complete response. Patients were evaluated by a multidisciplinary team including a thoracic surgeon, a medical oncologist, a radiation oncologist, a radiologist and a gastroenterologist. Pretreatment staging evaluation included physical and endoscopic examinations, contrast-enhanced computed tomography (CT) scans from the neck to upper abdomen, and/or endoscopic ultrasound (EUS). The tumor node metastasis stages (TNM) were determined according to the 7th American Joint Committee on Cancer (AJCC) staging system [18].

Table 1. Clinicopathologic features of 101 patients with esophageal squamous cell carcinoma receiving neoadjuvant chemoradiotherapy followed by surgery

Parameters	No. of cases (percentage)
Age (years)(mean: 52.87 , median: 52 , range: 44 (33-77))	
＜50	41 (40%)
50≦ Age＜60	35 (35%)
60≦ Age＜70	20 (20%)
70≦ Age	5 (5.0%)
Sex	
Male	99 (98%)
Female	2 (2%)
Clinical 7th AJCC stage	
II	19 (19%)
III	82 (81%)
Clinical T stage	
T1	0
T2	2 (2%)
T3	52 (52%)
T4	47 (46%)
Clinical N stage	
N0	20 (20%)
N1	41 (40%)
N2	30 (30%)
N3	10 (10%)
Pathologic 7th AJCC stage	
Complete response	26 (26%)
I	8 (8%)
II	41 (40%)
III	24 (24%)
IV	2 (2%)
Pathologic T stage	
T0	29 (29%)
T1	11 (11%)
T2	22 (22%)
T3	27 (26%)
T4	12 (12%)
Pathologic N stage	
N0	70 (69%)
N1	27 (27%)
N2	3 (3%)
N3	1 (1%)
Tumor grade	
1	24 (24%)
2	55 (54%)
3	22 (22%)
Primary tumor location	
Upper	20 (20%)
Middle	43 (42%)
Lower	38 (38%)

Table 2. Associations between pathologic complete response and clinicopathologic factors in 101 patients with esophageal squamous cell carcinoma receiving neoadjuvant chemoradiotherapy followed by surgery

		Pathologic complete response		
Parameters		Present	Absent	P value
Age				
	≦52 y/o	11	42	0.23
	＞52 y/o	15	33	
Clinical 7th AJCC stage				
	II	6	20	0.42
	III	20	63	
Clinical T stage				
	T1+2+3	16	38	0.34
	T4	10	37	
Clinical N stage				
	N0	7	13	0.29
	N1+2+3	19	62	
Tumor grade				
	1	9	15	0.13
	2+3	17	60	
Primary tumor location				
	U	4	16	0.51
	M+L	22	59	

CRT, chemoradiotherapy; *Statistically significant. x^2 test or Fisher's exact test was used for statistical analysis

Treatment Plan

Patients were concurrently treated with two cycles of cisplatin and 5-fluorouracil-based chemotherapy and radiotherapy (36 Gy in 20 fractions). Each cycle lasted between 3 and 4 weeks. Radiotherapy was delivered in five daily fractions per week of 1.8 Gy during the 4 weeks, and three-dimensional conformal radiotherapy (CRT) via a four-field technique was used for most of the patients. The gross tumor volume (GTV) was defined as the gross tumor and lymph nodes on the simulation CT scan. The clinical target volume (CTV) covered the GTV with a 3-cm craniocaudal margin and a 1-cm radial margin and also the entire mediastinal lymph nodes. For the upper or lower third primaries, bilateral supraclavicular lymph nodes or celiac lymph nodes were also included for prophylactic irradiation. The planning target volume was generated from the CTV with a 1-cm expansion in all directions. The radiotherapy was delivered by LINAC using 6- or 15-MV photons with 1.8 Gy per daily fraction, five fractions per week for a total dose of 36 Gy/20 fractions. After 2009, however, we modified the radiation dose to 50.4 Gy/ 28 fractions. Within 3-4 weeks following the end of irradiation, CT scans and endoscope were performed to assess the treatment response. Then, the multidisciplinary team reviewed the clinical information to determine if the lesions were resectable. If lesions were classified as resectable, surgery was advised 4-6 weeks after the end of preoperative chemoradiotherapy. Patients re-

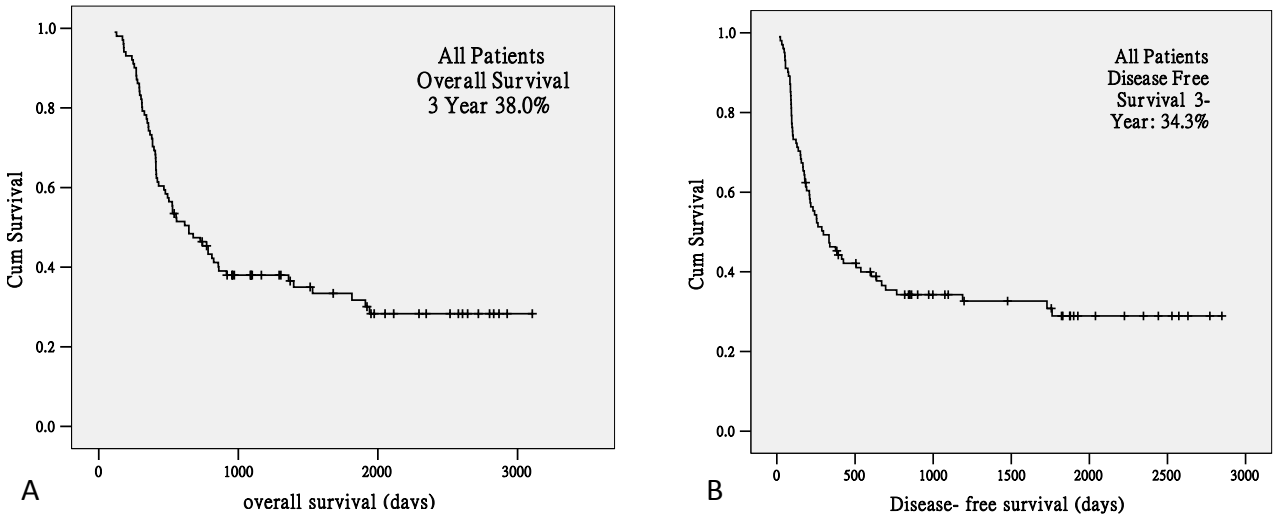

Figure 1. Overall survival (A) and disease-free survival (B) in 101 patients with esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy followed by surgery

ceiving surgery underwent a radical esophagectomy by video-assisted thoracoscopic surgery with cervical esophagogastrostomy or an Ivor Lewis esophagectomy with intrathoracic anastomosis, two-field lymphadenectomy and reconstruction of the digestive tract with gastric tube. Pathologic complete response was defined as the complete disappearance of all viable cancer cells in all surgical specimens, including the primary esophageal tumor and lymph nodes.

Follow Up

After the operation, patients were scheduled for follow-ups at 3-month intervals in years 1 and 2, 6-month intervals in years 3 to 5, and annually thereafter. Overall survival (OS) was calculated from the date of diagnosis to death as a result of all causes. Disease-free survival (DFS) was computed from the time of surgery to the recurrence or death from any cause without evidence of recurrence.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, ver. 13.0, Chicago, IL, USA), and the χ^2 test or Fisher's exact test were used to compare data between the two groups. For survival analysis, the Kaplan-Meier method was used for univariate analysis, and the difference between survival curves was tested by a log-rank test. In a stepwise forward fashion, parameters with $P < 0.1$ at the univariate level were in principle entered into a Cox regression model to analyze their relative prognostic importance. However, as component factors of the 7th AJCC staging system, the 7th T stage and 7th N stage were not introduced in multivariate analyses simultaneously. For all analyses, two-sided tests of significance were used with $P < 0.05$ considered to be significant.

RESULTS

Patient Characteristics

A total of 101 patients were included in the study with a median age of 52 years (range, 33-77 years). Among them, 99 were men and 2 were women. The pretreatment analyses of the clinical tumor stage revealed T2 in 2 patients (2%), T3 in 52 patients (52%), and T4 in 47 patients (46%). Additional pretreatment analyses according to the AJCC staging system demonstrated clinical stage II tumors for 19 patients (19%) and clinical stage III for 82 patients (81%).

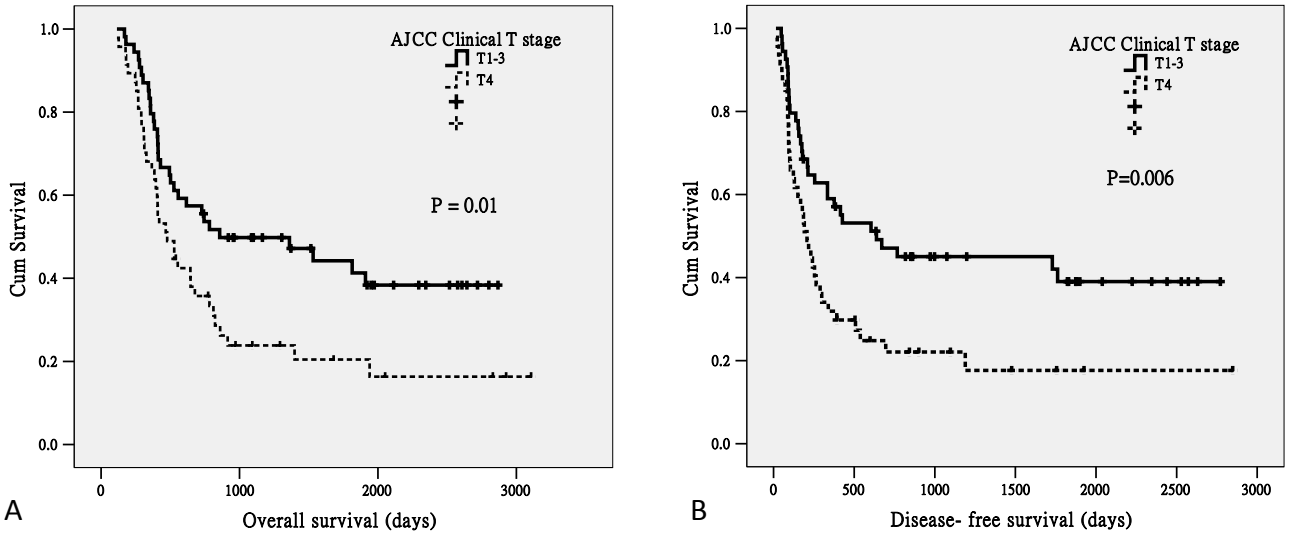

Figure 2. Overall survival (A) and disease-free survival (B) according to pretreatment clinical T stage

Further analyses of histological grades showed a grade 1 lesion in 24 patients, grade 2 in 55 patients, and grade 3 in 22 patients. Primary tumor location was found to be upper in 20 patients (20%), middle in 43 patients (43%), and lower in 38 patients (38%). Among these 101 patients, 26 achieved pathologic complete response after preoperative chemoradiotherapy (Table 1). The 3-year OS and DFS of these 101 patients were 38.0% and 34.3% (Figure 1, A and B), respectively. The median periods of follow-up were 64 months (range, 18.0-103.5 months) for the 33 survivors and 21.0 months (range, 3.8-103.5 months) for all 101 patients.

Correlation between Clinicopathologic Parameters and Pathologic Complete Response

We did not observe significant correlation between pathologic complete response with age, clinical AJCC stage, clinical T stage, clinical N stage, tumor grade, and primary tumor location (Table 2).

Survival Analyses of all 101 Patients

Univariate analyses demonstrated that clinical T stage (3-year OS rate, 50% vs 24% , P =0.01; 3-year DFS rate, 45% vs 22% , P = 0.006; Figure 2, A and B), and pathologic complete response (3-year OS rate, 28% vs 68% , P= 0.001; 3-year DFS rate, 23% vs 68 % , P < 0.001) were associated with the inferior OS and DFS (Table 3). But, we did not observe significant correlation between OS and DFS with age, clinical N stage, tumor grade, and primary tumor location (Table 3). In multivariate analysis, clinical T stage was an independent prognosticator for overall survival (P = 0.012, odds ratio: 1.854, 95% confidence interval: 1.146-3.000) and disease-free survival (P = 0.008, odds ratio: 1.94, 95% confidence interval: 1.192-3.158). Pathologic complete response was also an independent prognosticator for overall survival (P = 0.001, odds ratio: 3.169, 95% confidence interval: 1.567-6.412; Figure 3A) and disease-free survival (P = 0.001, odds ratio: 3.326, 95% confidence interval: 1.643- 6.734; Figure 3B).

Survival Analyses of 74 Patients who did not Reach Pathologic Complete Response

We also performed subgroup survival analysis on 74 patients who did not reach pathologic complete response. Univariate analysis demonstrated that clinical T stage (3-year OS rate, 42 % vs 14%, P = 0.004;

Table 3. Results of univariate log-rank analysis of prognostic factors for overall survival and disease-free survival in 101 patients with esophageal squamous cell carcinoma receiving neoadjuvant chemoradiotherapy followed by surgery

Factors	No. of patients	Overall survival (OS)		Disease-free survival (DFS)	
		3-year OS rate (%)	P value	3-year DFS rate (%)	P value
Age					
<52 y/o	53	35%	0.59	30%	0.62
≧52 y/o	48	42%		38%	
Clinical 7th AJCC stage					
II	19	58%	0.16	52%	0.12
III	82	33%		30%	
Clinical T stage					
T1+2+3	54	50%	0.01*	45%	0.006*
T4	47	24%		22%	
Clinical N stage					
N0	20	50%	0.50	44%	0.37
N1+2+3	81	35%		32%	
Tumor grade					
1	24	32%	0.65	32%	0.48
2+3	77	40%		35%	
Primary tumor location					
Upper	20	41%	0.40	23%	0.48
Middle/Lower	81	25%		37%	
Pathologic CR					
Absent	75	28%	0.001*	23%	0.000*
Present	26	68%		68%	

CR, complete response; *Statistically significant

3-year DFS rate, 36% vs 10%, P = 0.003), pathologic AJCC stage (3-year OS rate, 35 % vs 15%, P =0.015; 3-year DFS rate, 31% vs 6%, P = 0.001) and pathologic T stage (3-year OS rate, 44% vs 15%, P = 0.000; 3-year DFS rate, 38% vs 10%, P = 0.000) were associated with inferior OS and DFS. The univariate analysis are summarized in Table 4. In multivariate analysis, clinical T stage was an independent prognosticator for overall survival (P = 0.015, odds ratio: 1.885, 95% confidence interval: 1.133-3.137) and disease-free survival (P = 0.011, odds ratio: 1.971, 95% confidence interval: 1.171-3.315). Pathologic T stage was also an independent prognosticator for overall survival (P = 0.001, odds ratio: 2.655, 95% confidence interval:

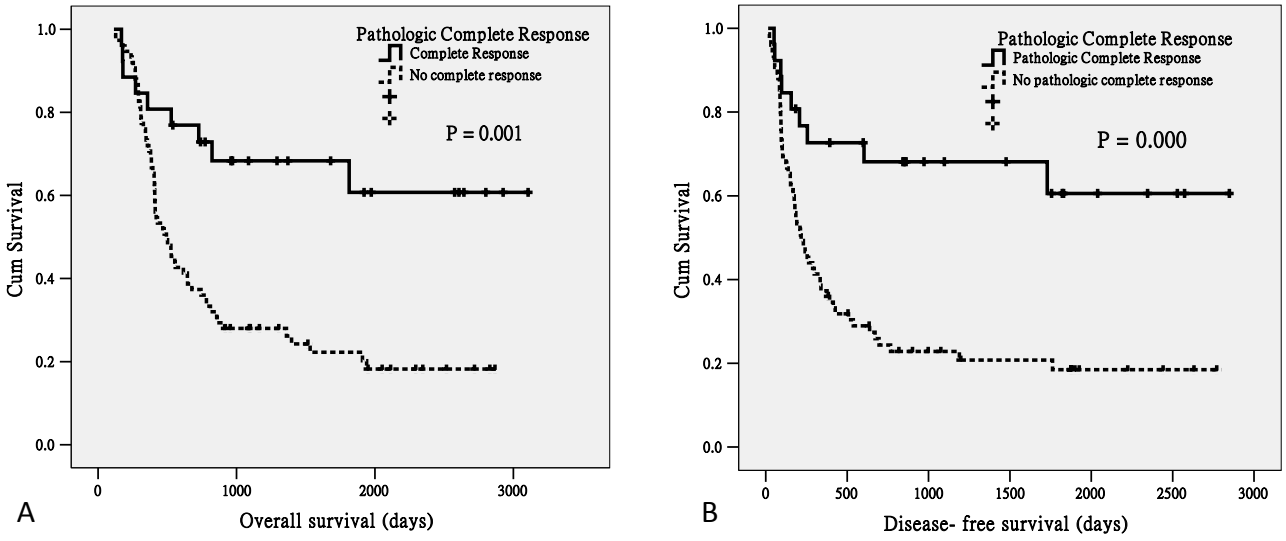

Figure 3. Overall survival (A) and disease-free survival (B) according to the response of preoperative chemoradiotherapy

1.532-4.600) and disease-free survival (P = 0.000, odds ratio: 2.711, 95% confidence interval: 1.563-4.703).

DISCUSSION

Esophageal squamous cell carcinoma is usually diagnosed at an advanced stage [19,20]. The outcome of patients with locally advanced esophageal squamous cell carcinoma treated with surgery alone is unsatisfactory, despite recent improvements in technique and perioperative management of patients [5]. In an attempt to improve survival rates, multimodality approaches such as preoperative chemoradiotherapy followed by surgery have been advocated to treat locally advanced esophageal squamous cell carcinoma [9,10, 17]. Previous series reported that the 3-year OS in patients with esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy followed by surgery ranged from 26 to 39% [8,21]. In our series, the 3-year OS was 38%, which is similar to the survival rate observed in the previous report.

After preoperative chemoradiotherapy, previous studies showed that pathologic complete response can be found in 20-40% of resected esophageal tumor specimens. There have been indications of a noteworthy therapeutic long-term benefit to achieving a pathologic complete response. Multiple retrospective series have reported 5-year survivals of 40-60% in those groups of patients when compared with those with specimens containing residual disease [22-25]. In our series, pathologic complete response was found in 27% of patients, and the 3-year overall survivals were 68% and 28% in patients with and without pathologic complete response, respectively (P =0.001); these results further support the previous findings. On the other hand, with the development of chemoradiotherapy, a surrogate marker of treatment efficacy becomes important. If tumors can be sterilized after chemoradiotherapy, surgery may not be necessary as it can lead to additional postoperative mortality and morbidity [26]. Otherwise, surgery is strongly suggested to eradicate local-regionally residual disease or may be taken into consideration as first treatment modality if the tumor is resectable. Therefore, there is an urgent need to identify patients who are likely or unlikely to respond to chemoradiotherapy. If we can find factors that predict the effect of chemoradiotherapy, a more effective therapeutic strategy can be expected.

Table 4. Results of univariate log-rank analysis of prognostic factors for overall survival and disease-free survival in patients with esophageal squamous cell carcinoma receiving neoadjuvant chemoradiotherapy followed by surgery which did NOT achieve pathologic complete response

Factors	No. of patients	Overall survival (OS)		Disease-free survival (DFS)	
		3-year OS rate (%)	P value	3-year DFS rate (%)	P value
Age					
<median 52 y/o	42	24%	0.31	18%	0.37
≧median 52 y/o	33	33%		29%	
Clinical 7th AJCC stage					
II	12	42%	0.40	30%	0.36
III	63	26%		22%	
Clinical T classification					
T1+2+3	38	42%	0.004*	36%	0.003*
T4	37	14%		10%	
Clinical N status					
N0	13	39%	0.50	27%	0.36
N1+2+3	62	26%		23%	
Pathological 7th AJCC stage					
I+II	49	35%	0.015*	31%	0.001*
III+IV	26	15%		6%	
Pathological T classification					
T0+1+2	36	44%	0.000*	38%	0.000*
T3+4	39	15%		10%	
Pathological N status					
N0	44	32%	0.72	29%	0.57
N1+2+3	31	23%		15%	
Tumor grade					
1	15	20%	0.48	20%	0.55
2+3	60	31%		24%	
Primary tumor location					
Upper	16	19%	0.51	16%	0.71
Middle/Lower	59	31%		25%	

CR, complete response; *Statistically significant

In our series, pretreatment clinical T4 disease was an independent prognosticator for overall survival and disease-free survival in all 101 patients. For 75 patients who did not achieve pathologic complete response, pretreatment clinical T4 disease and pathologic T3~4 disease were also an independent prognosticators for overall survival and disease-free survival. Kim et al. [27] and Chao et al. [28] also reported that pretreatment clinical stage is an important prognostic marker for survival, even though patients achieved major response after preoperative chemoradiotherapy. These results suggest that adjuvant chemotherapy after esophagectomy may be considered in these group of patients.

In conclusion, clinical T4 disease and the absence of pathologic complete response were associated with significantly worse survival in patients with esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy followed by surgery in this retrospective analysis. Future studies should focus on the role of modalities in restaging after preoperative chemoradiotherapy to determine which patients will benefit from further esophagectomy. Additionally, it is important to further explore the biologic differences between patients with and without pathologic complete response.

REFERENCES

1. Stoner GD, Gupta A. Etiology and chemoprevention of esophageal squamous cell carcinoma. **Carcinogenesis 22:** 1737-1746, 2001.
2. Mandard AM, Hainaut P, Hollstein M. Genetic steps in the development of squamous cell carcinoma of the esophagus. **Mutat Res 462:** 335-342, 2000.
3. Gockel I, Kneist W, Junginger T. Incurable esophageal cancer: patterns of tumor spread and therapeutic consequences. **World J Surg 30:** 183-190, 2006.
4. Siewert JR, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? **Semin Radiat Oncol 17:** 38-44, 2007.
5. Sherman CA, Turrisi AT, Wallace MB, et al. Locally advanced esophageal cancer. **Curr Treat Options Oncol 3:** 475-485, 2002.
6. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. **Ann Surg 236:** 376-384; discussion 384-375, 2002.
7. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. **J Clin Oncol 26:** 1086-1092, 2008.
8. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. **N Engl J Med 337:** 161-167, 1997.
9. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. **J Clin Oncol 23:** 2310-2317, 2005.
10. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. **J Clin Oncol 25:** 1160-1168, 2007.
11. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. **World J Surg 16:** 1104-1109; discussion 1110, 1992.
12. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. **N Engl J Med 335:** 462-467, 1996.
13. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. **Lancet**

Oncol 6: 659-668, 2005.

14. Lee JL, Park SI, Kim SB, et al. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. **Ann Oncol 15:** 947-954, 2004.
15. Natsugoe S, Okumura H, Matsumoto M, et al. Randomized controlled study on preoperative chemoradiotherapy followed by surgery versus surgery alone for esophageal squamous cell cancer in a single institution. **Dis Esophagus 19:** 468-472, 2006.
16. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. **J Clin Oncol 19:** 305-313, 2001.
17. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. **Lancet Oncol 8:** 226-234, 2007.
18. Edge S, Byrd DR, Compton CC, et al. eds. Esophagus and esophagogastric junction. In: AJCC Cancer Satging Manual. 7th ed. New York: Springer; 103-11, 2010.
19. Report. CRA National Department of Health, Taiwan, Republic of China, 2007 Available from: URL: http://wwwbhpdohgovtw/BHPNET/Portal/StatisticsShowaspx?No=200911300001.
20. Chung CS, Lee YC, Wang CP, et al. Secondary prevention of esophageal squamous cell carcinoma in areas where smoking, alcohol, and betel quid chewing are prevalent. **J Formos Med Assoc 109:** 408-421, 2010.
21. Apinop C, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. **Hepatogastroenterology 41:** 391-393, 1994.
22. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. **J Clin Oncol 23:** 4330-4337, 2005.
23. Donington JS, Miller DL, Allen MS, et al. Tumor response to induction chemoradiation: influence on survival after esophagectomy. **Eur J Cardiothorac Surg 24:** 631-636; discussion 636-637, 2003.
24. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. **J Clin Oncol 23:** 4330-4337, 2005.
25. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. **J Clin Oncol 23:** 2310-2317, 2005.
26. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. **J Clin Oncol 24:** 4277-4284, 2006.
27. Kim MK, Cho KJ, Park SI, et al. Initial stage affects survival even after complete pathologic remission is achieved in locally advanced esophageal cancer: analysis of 70 patients with pathologic major response after preoperative chemoradiotherapy. **Int J Radiat Oncol Biol Phys 75:** 115-121, 2009.
28. Chao YK, Chan SC, Liu YH, et al. Pretreatment T3-4 stage is an adverse prognostic factor in patients with esophageal squamous cell carcinoma who achieve pathological complete response following preoperative chemoradiotherapy. **Ann Surg 249:** 392-396, 2009.